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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/484,895	HARRINGTON ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2003 and 25 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58,61-109 and 113-121* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *118* is/are allowed.

6)☒ Claim(s) *58,61-65,67-70,72-109,113-116 and 119-121* is/are rejected.

7)☒ Claim(s) *66,71 and 117* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *20* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendments filed on 8/27/03 and 07/25/03 have been entered.

Amended claims 58, 61-109 and 113-121 are pending in the present application, and they are examined on the merits herein.

REMARK

The reference, Burgess et al, referred **ambiguously** by Applicants in the amendment filed on 8/27/03 without citing the name of the journal or document, the year or page numbers, is the WO 99/07389. The identity of the reference was confirmed by Mr. Jonathan Sparks after telephonic inquiries made by Examiner on 9/25/03 and 9/29/03.

Following is a new ground of rejection necessitated by Applicants' amendment.

New Matter

Amended claims 58, 61-64, 72-96, 100-109 and 119 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 58 recites "contains a translational start codon that is not operably linked to a translational stop codon". There is literal no support in the originally filed

specification that Applicants contemplate specifically to introduce the recited limitation in the vector. While the specification teaches in general a vector construct with a regulatory sequence and an exon containing a translation start codon in reading frame 1 (relative to the splice donor site), followed by an unpaired splice donor site (see page 38, construct 3 as pointed out by Applicants for the support of the amendment filed on 8/27/03), there is no literal written support that Applicants contemplate specifically to make and use a vector construct that contains a translational start codon that is not operably linked to a translational stop codon as claimed at the time the application was filed. Therefore, given the lack of written support in regarding to the aforementioned issue, it would appear that Applicants did not have possession of the claimed invention at the time the application was filed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 58, 61-64, 72-96, 100-109 and 119 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth immediately above. As enablement requires the specification to teach how to make and use the claimed invention, with the lack of sufficient description and/or

guidance provided by the instant specification at the time the application was filed regarding to the make and use of a vector having the limitations recited in claim 58, it would have required undue experimentation for a skilled artisan to make and use the presently claimed invention.

Amended claims 106-107 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing a protein in a eukaryotic cell having the steps recited in claim 106, does not reasonably provide enablement for a method for producing a protein in any cell in which splicing can occur. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the same reasons already set forth in the previous Office Action.

Response to Arguments

Applicants' argument related to the above rejections in the Amendment filed on 07/25/03 (pages 19-20) have been fully considered, but they are not found persuasive.

Applicants argue mainly that although native prokaryotes do not contain splicing enzymes and DNA which is normally spliced, it is possible to transfect prokaryotic cells with eukaryotic DNA and transfect the cells with genes that express splicing enzymes. In this way, using Applicants' vectors and isolated genomic DNA, the method could

potentially be practiced in cells that do not normally regulate their own genes by splicing.

It is noted that the vectors in the methods as claimed contain only promoters that are functional in a eukaryotic cell, and therefore these vectors are not functional in prokaryotic cells even the prokaryotic cells are transfected or transformed with genes that express splicing enzymes. Moreover, the methods as claimed do not recite the essential step of transfecting or transforming prokaryotic cells with genes that express splicing enzymes. Should Applicants decide to introduce this limitation, please cite specific page number, line number of the specification to support such amendment. Furthermore, Applicants also state that the method could potentially be practiced in cells that do not normally regulate their own genes by splicing.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Amended claims 58, 61-65, 73, 76, 78-79, 81, 84-87, 89, 92 and new claims 120-121 are rejected under 35 U.S.C. 102(e) as being anticipated by Treco et al. (U.S.

Patent No. 6,270,989) for the same reasons already set forth in the previous Office Action.

Treco et al. disclose the preparation of a targeting construct (pRTPO1) comprising in the following order a selectable marker *neo* gene (derived from the bacterial neomycin phosphotransferase gene that may contain an endogenous promoter and without a polyadenylation signal), a mouse dihyrodrofolate reductase (dhfr) gene (an amplifiable marker gene), a regulatory sequence (e.g., CMV promoter) operatively linked to an exon flanked by an unpaired splice donor site at the 3' end of the exon, wherein the exon includes a CAP site and non-coding sequences or contains an ATG translation initiation codon in-frame with the coding sequences of the endogenous genes or encodes a sequence including portion of a signal peptide designed to improve cellular secretion, leader sequences, transmembrane domains and others (see Fig. 6 and cols. 10-14). Treco et al. further teach the DNA constructs to be introduced into cells to activate cellular endogenous genes under conditions suitable for homologous recombination (see col. 14).

Accordingly, the teachings of Treco et al. meet the limitations of the claims, and therefore the reference anticipates the instant claims.

Response to Arguments

Applicants' argument related to the above rejections in the Amendment filed on 07/25/03 (page 22) have been fully considered, but they are not found persuasive.

Applicants argue mainly that pRTOP1 contains a polyadenylation signal operably-linked to the DHFR and Neo gene, and further supports Applicants' assertion by a schematic diagram drawn by Applicants in Attachment B.

It is noted that that Fig. 6 in the issued U.S. 6,270,989 does not indicate a polyA signal in the *neo* gene. More over, as already explained above that the *neo* gene is derived from the bacterial neomycin phosphotransferase gene that normally does not contain a polyadenylation signal. Furthermore, Treco et al. teach specifically that the positively selectable marker *neo* is used to select for cells, including eukaryotic cells particularly for cells that are capable of mediating homologous recombination, which have stably incorporated the DNA of the targeting construct (col. 13, lines 28-31). Therefore, the *neo* gene in the pRTOP1 is also operabably linked to a promoter that is functional in a eukaryotic cell.

Claims 70, 73-79, 81-87, 89-92 and 113-116 are rejected under 35 U.S.C. 102(b) as being anticipated by Treco et al. (WO 95/31560; IDS). **This is a new ground of rejection.**

Treco et al. disclose the preparation of DNA constructs useful in the method of altering expression of a target gene, said constructs comprise: (a) a targeting sequence; (b) a regulatory sequence; (c) an exon; and (d) an unpaired splice-donor site, wherein

the targeting sequence directs the integration of elements (a) to (d), such that the elements (b) to (d) are operatively linked to the endogenous gene. Treco et al. teach also that the regulatory sequence can be comprised of one or more promoters, and the DNA construct comprises one or more exons (preferably containing an ATG) and one or more selectable marker genes (both positive and negative selective marker genes) for identification of the targeting event, with the negative selective marker is linked to the exogenous DNA but configured such that the negatively selectable marker flanks the targeting sequence (line 34 of page 23 continues to line 12 of page 24; particularly page 26, lines 1-24). Positive selective markers include, neo, xanthine guanine phosphoribosyl transferase, dhfr, adenosine deaminase, puromycin, hygromycin, mdr1 and others (page 23, lines 22-31), while negative selective markers include herpes simplex virus thymidine kinase or bacterial gpt (page 24, lines 9-12). The DNA construct also comprises plasmid DNA sequences used for the selection and/or replication of the targeting plasmid in a microbial or other suitable host (line 32 of page 24 continues to line 4 of page 25; page 27, lines 15-19 and the Figures), an amplifiable positively selectable marker (e.g., ada, GS, dhfr, CAD gene and others, see page 24, lines 22-29, page 26, lines 25-34). The DNA construct is introduced into cells under conditions which permit homologous recombination, so that homologously recombinant cell is maintained under conditions sufficient for transcription of the DNA (page 28, lines 12-20).

Since the DNA constructs of Treco et al. are also capable of incorporating randomly into a cell genome, and that the negatively selective marker genes must

contain a promoter for the expression of negatively selective markers in eukaryotic cells for the identification of proper homologously recombinant cells, the DNA constructs of Treco et al. meet the limitation recited for the vectors of the presently claimed invention. It should be noted that the negatively selective marker genes of the DNA constructs of Treco et al. which have been incorporated randomly into genomes of transfected cells would also be deleted through a splicing event due to the presence of the unpaired splice donor site.

Therefore, Treco et al. (WO 95/31560) anticipate the instant claims.

Claims 67-69, 74-75, 77, 79, 82-83, 85-87, 90-91, 94-96, 97-101 and 119 are rejected under 35 U.S.C. 102(e) as being anticipated by Burgess et al. (U.S. Patent No 6,139,833; IDS). **This is a new ground of rejection.**

Burgess et al. teach an LTR vector, VICTR12, comprising a PGK promoter operably linked to a puromycin gene which is operably linked to an unpaired splice donor sequence at both of the vector long terminal repeats (see Fig. 2), and a collection of eukaryotic cells or a library of cells whose genomes contain the insertion of this vector (col. 7, line 55 continues to line 18 of col. 8). The puromycin gene is used as a selectable marker, and it does not contain a polyadenylation signal (col. 21, line 45 continues to line 10 of col. 22). Additionally, Burgess et al. teach a method that allows for rapid identification, cloning, sequencing of genes trapped by the vector (col. 22, lines 45-64; col. 24, lines 47-61, particularly sections 5.5 to 5.7 in cols. 35-38). Burgess et al. also teach that features of the disclosed gene trapping vector are not limited to the LTR

vector, and that different types of vectors that may also be used to incorporate relatively small engineered exons into a target cell transcripts, including SV40 based vectors, adenovirus vectors, adeno-associated virus vectors and others (col. 23, lines 55-62).

Accordingly, the teachings of Burgess et al. meet the limitations of the instant claims, and therefore the reference anticipates the instant claims.

Conclusion

Claim 118 is allowed.

Claims 66, 71 and 117 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

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